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Der Pharmacia Sinica, 2010, 1 (1): 147-165

Hydrophilic polymers matrix systems of Nifedipine sustained release matrix tablets: Formulation optimization by Response Surface Method (Box-Behnken technique)

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ABSTRACT

The modified release matrix dosage form is preferred in order to avoid fluctuations in the blood levels, which was observed in the drug Nifedipine. The aim of the present research was to formulate a sustained release matrix dosage form of Nifedipine, a potent therapeutic agent for cardiovascular disease, which primarily reduce the occurrence of steep rises in plasma concentration of drug, by using different polymers to achieve better bioavailability and also to reduce dosing frequency and side-effects employing response surface methodology by incorporating a 3-factor, 3-level Box-Behnken statistical design. Dependent variables are the release retardant polymers such as HPMC K15M (X_1), HPMC E10 CR Prem. (X_2), and Sodium Alginate (X_3) and Independent variables are the percentage drug release at 1 h (Y_1), percentage drug release at 8 h (Y_2) and hardness (Y_3) were studied. Box-Behnken response surface plots were drawn, statistical validity of the second order and quadratic models were established and the optimized formulations was chosen based on feasibility and grid search. The physical evaluation and in-vitro release studies were performed on all the formulations and the data were fitted to different release kinetic equations such as zero order, first order, Higuchi, Hixson Crowell and Korsemayer-peppas in terms of r^2 and n-value. Validation of the optimization study with 13 confirmatory runs indicated high degree of prophetic ability of response surface methodology. From the confirmatory runs, the optimized formulation showed gradual sustained release (best fit model–peppas, n=0.44) by Fickian diffusion process. This design facilitated the optimization of Nifedipine sustained release matrix dosage form to achieve better bioavailability.

Key words: Nifedipine, Sustained release, Response surface methodology, Box-Behnken design, Variables, Responses.

INTRODUCTION

In India, 2.3 million deaths were recorded caused by CVD in 1990, which may double by the year 2020. Thus, the management of CVD becomes very important to improve the health care system[1]. Several drugs are being prescribed for the successful management of cardio vascular diseases (CVD), among the various drugs, Nifedipine, a dihydropyridine derivative, is effectively being used drug in the management of various CVDs such as angina, mild to moderate hypertension, myocardial infraction, etc[2]. Nifedipine is a suitable drug candidate for sustained release administration due to its short elimination half-life of 2 to 4 h, its rapid and complete drug absorption over the entire gastrointestinal tract, despite its low water solubility (10mg/l), and the relationship between drug plasma concentrations and blood pressure reduction[3,4]. The importance of reduced peak plasma level of this drug in order to avoid adverse effects such as reflex tachycardia has also been reported[5].

Many strategies are available for the design and development of sustained release drug delivery formulations. The primary purpose of these drug delivery devices is to improve the state of disease management by modifying the pharmacokinetic profiles of therapeutic agents normally administered as conventional tablets or capsules. Conventional oral dosage forms often produce fluctuations of drug plasma level that either exceed safe therapeutic level or quickly fall below the minimum effective level; this effect is usually totally dependent on the particular agent's biologic half-life, frequency of administration and release rate. It is recognized that many patients can benefit from drugs intended for chronic administration by maintaining plasma levels within a safe and effective range[6]. Different grades of Hydroxypropylmethylcellulose (HPMC) and Sodium alginate are a few representative examples of the hydrophilic polymers that have been extensively used in the formulation of controlled release matrix system. HPMC a semisythetic derivative of cellulose and sodium alginate a natural polymer which are popular as a swellable and hydrophilic polymers. It's a non-toxic nature and ease of handling makes it an excellent release retardant material. On exposure to aqueous fluids, the polymers hydrate to form a viscous gel layer through which the drug is releasd by diffusion and/or erosion of the matrix[7-9].

Response surface methodology (RSM) is one of the popular methods in the development and optimization of drug delivery systems. Based on the principles of design of experiments (DOE), the methodology involves the use of various types of experimental designs, generation of polynomial mathematical relationships and mapping of the response over the experimental domain to select the optimum formulation[10-12]. Central composite design[13,14] (CCD) and 3-level factorial design, Box Behnken design[13] and D-optimal design[15] are the different types of RSM designs available for statistical optimization of the formulations. Box-Behnken statistical design is one type of RSM design that is an independent, rotatable or nearly rotatable, quadratic design having the treatment combinations at the midpoints of the edges of the process space and at the center[16-18]. Additionally, it requires fewer experimental runs and less time and thus provides a far more effective and cost-effective technique than the conventional processes of formulating and optimization of dosage forms.

The present investigation aimed at developing and optimizing an oral sustained release dosage form of Nifedipine using computer-aided optimization technique i.e. Box Behnken statistical

design with constraints on cumulative percentage release of drug after 8 h (70-75%). The Independent variables are the amount of release retardant polymers such as HPMC K15M, (X_1), HPMC E10 CR Prem., (X_2) and Sodium Alginate, (X_3) and the dependent variables are the burst release in 1h (Y_1), cumulative percentage release of drug after 8 h (Y_2) and hardness of the tablets (Y_3) were studied.

MATERIALS AND METHODS

Nifedipine was provided by Sai Mirra Pharmaceuticals, Chennai, India. HPMC K15M and HPMC E10 PCR, were received as gift sample from colorcon Asia (Pvt) Ltd, Mumbai, India. Microcrystallinecellulose and Magnesium stearate was purchased from S.D Fine Chemicals, Mumbai, India. Sodium Alginate was purchased from Kemphasol, Mumbai. Aerosil and other additives were used as AR grade purchased from S.D Fine Chemicals and Himedia Chemie, India.

Analytical method development

The stock solution of the drug was prepared with methanol and phosphate buffer pH 6.8 (1:1 ratio) and further dilution with phosphate buffer pH 6.8. The drug absorbance was measured at 235nm using UV double beam spectrophotometer (UV100 cyber Lab). The linearity of the absorbance was found to be from the concentration between 10–50µg/ml ($r^2 = 0.9938$).

Computer aided optimization design

Response surface methodology optimization technique using a 3-factor, 3-level design (Box and Behnken, 1960) was employed for the optimization study. This design is suitable for exploration of second order polynomial model, quadratic response surfaces, thus helping in optimizing a process using a small number of experimental runs(17 runs) with Design expert (version 8.0.1, stat-ease inc., Minneapolis, MN). This cubic design is characterized by set of points lying at the midpoint of each edge of a multi-dimensional cube and centre points replicates (n=5). The polynomial equations for different models are given below,

Linear model;

$$Y = A_1 X_1 + A_2 X_2 + A_3 X_3$$

Quadratic model;

$$Y = A_0 + A_1 X_1 + A_2 X_2 + A_3 X_3 + A_{12} X_1 X_2 + A_{13} X_1 X_3 + A_{23} X_2 X_3 + A_{11} X_1^2 + A_{22} X_2^2 + A_{33} X_3^2$$

Second order;

$$Y = A_1 X_1 + A_2 X_2 + A_3 X_3 + A_{12} X_1 X_3$$

The Y is the measured response associated with each factor level combination; A_0 is an intercept; A_1 to A_{33} are regression coefficients computed from the observed experimental values of Y; and X_1, X_2 and X_3 are the coded levels of independent variables. The terms X_1X_2 and X^2_n (n = 1, 2 or

3) represent the interaction and quadratic terms, respectively[19]. The preliminary studies provided a setting of the levels for each formulation. Three variables and three responses were involved in this optimization design. The variables and their different levels studied, the high and low values of each variable were defined based on preliminary experiments are summarized in Table 1.

Table 1. Different levels of variables used in the formulations

Dependent Variables	Different levels (actual is coded)		
	Low	**Medium**	**High**
X_1 – HPMC K15M	10 (-1)	20 (0)	30 (+1)
X_2 – HPMC E10 PCR.	20 (-1)	30 (0)	40 (+1)
X_3 – Sodium Alginate	1 (-1)	3 (0)	5 (+1)

Independent variables	**Constraints**
Y_1 - % Dissolution after 60min	$20 \leq Y1 \leq 25$
Y_2 - % Dissolution after 8 hrs	$70 \leq Y2 \leq 75$
Y_3 – Hardness(kg/cm^2)	3.5 – 5

Preparation of matrix tablets

Matrix tablets (17 formulations proposed by response surface model - Box-Behnken design) each containing 20mg of Nifedipine were prepared with matrix former such as HPMC K15M, HPMC E10 PCR and Sodium alginate in different ratio by direct compression technique. The ingredients previously sieved (#60mesh) are mixed in a planetary mixer for 15 min and the tablets were punched using 6mm punches in high speed 8 station rotary tablet machine. Factor combination as per the experimental design is tabulated in Table 2. The amount of variables used to formulate 17 formulations as per the Box-Behnken design in Table 3.

Table 2. Factor combination as per the experimental design

Trial factor	Coded factor level		
	X_1	**X_2**	**X_3**
1	0	0	0
2	0	-1	-1
3	-1	0	-1
4	0	0	0
5	0	0	0
6	0	-1	1
7	0	0	0
8	0	1	1
9	-1	-1	0
10	1	0	-1
11	1	0	-1
12	-1	0	1
13	1	0	1
14	0	0	0
15	0	1	-1
16	1	-1	0
17	-1	1	0

Table 3. The working formula for 17 formulations as per the Box-Behnken design

Formulation/ Ingredients	Nifedipine (mg)	HPMC K15M(mg)	HPMC E10PCR(mg)	Sodium Alginate(mg)	MCC (mg)	Aerosil (%)	Magnesium Sterate (%)
NF1	20	20	30	3	24	1	2
NF2	20	20	20	1	36	1	2
NF3	20	10	30	1	36	1	2
NF4	20	20	20	3	24	1	2
NF5	20	20	30	3	24	1	2
NF6	20	20	20	5	32	1	2
NF7	20	20	30	3	24	1	2
NF8	20	20	40	5	12	1	2
NF9	20	10	20	3	44	1	2
NF10	20	30	40	3	4	1	2
NF11	20	30	30	1	16	1	2
NF12	20	10	30	5	32	1	2
NF13	20	30	30	5	12	1	2
NF14	20	20	30	3	24	1	2
NF715	20	20	40	1	16	1	2
NF16	20	30	20	3	24	1	2
NF17	20	10	40	3	24	1	2

Physical evaluation of tablets

Drug content analysis

A quantity of tablet powder equivalent to label claim (20mg) of Nifedipine were taken for drug content analysis using methanol as extracting solvent and the samples were analyzed by using double beam spectrophotometer (Shimadzu uv-100) at 235nm. The drug content of the formulations was calculated by using the following formula. The assay values obtained are tabulated in Table 4.

$$\%\ \text{Drug content} = \frac{\text{Drug content}}{\text{Label claim}} \times 100$$

Physical evaluations

Tablets were evaluated for their hardness (n=6) using Monsanto hardness tester, friability (n=20) by using Roche Friabilator at100rpm, weight variation (n=20) and thickness (n=10)(zoom dial caliper). The physical evaluation values obtained are tabulated in Table 4.

Table 4. Drug content and Physical evaluation of 17 runs

S. No	Formulations	Weight variation (%)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug Content (%)
1	F1	1.004 ±0.06	4 .00±0.28	3.22 ±0.03	0.05 ±0.01	92.55 ±0.24
2	F2	1.006 ±0.05	4.33 ±0.28	3.44±0.04	0.05 ±0.01	92.55 ±0.24
3	F3	1.003 ±0.71	3.67 ±0.29	3.26±0.01	0.05 ±0.05	92.80 ±0.17
4	F4	1.001 ±0.26	3.67 ±0.29	3.46±0.03	0.10 ±0.02	93.95 ±0.33
5	F5	1.008 ±0.06	3.68 ±0.28	3.34±0.02	0.05 ±0.01	92.50 ±0.24
6	F6	1.002 ±0.45	4.50 ±0.28	3.55±0.04	0.04 ±0.01	95.70 ±0.39
7	F7	1.009 ±0.49	4.50 ±0.14	3.38±0.01	0.36 ±0.46	96.60 ±0.57

8	F8	1.009 ±0.64	3.83 ±0.02	3.34±0.05	0.10 ±0.01	92.65 ±0.12
9	F9	0.998 ±0.35	4.50 ±0.28	3.21±0.01	0.12 ±0.02	96.60 ±0.17
10	F10	1.001 ±0.29	4.16 ±0.02	3.44±0.02	0.11 ±0.02	95.50 ±0.09
11	F11	0.997 ±0.40	4.00 ±0.29	3.31±0.01	0.13 ±0.01	99.40 ±0.13
12	F12	1.008 ±0.40	4.50 ±0.28	3.34±0.01	0.12 ±0.02	94.75 ±0.17
13	F13	1.005 ±0.50	4.50 ±0.01	3.42±0.03	0.11 ±0.01	97.10 ±0.02
14	F14	0.999 ±0.26	5.00±0.14	3.16±0.02	0.09 ±0.01	97.70 ±0.27
15	F15	1.006 ±0.48	4.16 ±0.28	3.27±0.04	0.10 ±0.01	93.20 ±0.28
16	F16	1.002 ±0.05	5.00 ±0.28	3.32±0.01	0.05 ±0.01	92.55 ±0.24
17	F17	1.001 ±0.35	4.17 ±0.29	3.62±0.02	0.53 ±0.05	97.11 ±0.13

FTIR study

The FTIR spectra of drug raw material and polymer blend of optimized tablet, and polymers was recorded from 4000 – 400 as scanning range between wave number (cm^{-1}) and % Transmittance. Samples were prepared in KBr discs (2mg sample in 200mg KBr) with a hydrostatic press at a force of 5ι cm^{-2} for 5min and the resolution was 4 cm^{-1}. Experiments were duplicated to check the reproducibility.

***In-vitro* drug release study**

Dissolution studies were performed using USP (II) standard dissolution apparatus at 37 ± 1ºC. The Tablets in triplicate were placed in 900ml of dissolution medium pH 6.8 Phosphate buffer and rotated at 50 rpm. A 5ml of sample was withdrawn at specific time intervals of 30, 60, 90, 120, 150, 180, 240, 360 and 480min after each withdrawal, same volume of fresh dissolution medium was replaced to maintain sink conditions. The cumulative percentage drug release was calculated for the 17 formulations and the responses observed by Box-Behnken design are shown in Table 5.

Table 5. The 17 runs and the responses observed by Box-Behnken design

Runs	Dependent Variables			Independent Variables		
	X_1(%)	X_2(%)	X_3(%)	Y_1(%)	Y_2(%)	Y_3(kg/cm^2)
1	20	30	3	27.93	72.38	4.00
2	20	30	3	26.26	72.26	4.33
3	10	40	3	27.02	67.54	3.67
4	30	30	1	25.72	65.23	3.67
5	20	30	3	26.13	73.99	3.68
6	30	40	3	26.76	60.03	4.50
7	20	20	3	27.69	72.37	4.50
8	30	0	3	52.77	79.81	3.83
9	20	20	5	23.24	72.26	4.50
10	30	30	5	23.03	65.10	4.16
11	20	20	1	25.17	57.69	4.00
12	20	40	1	21.34	63.42	4.50
13	10	30	5	25.09	60.21	4.50
14	10	20	3	24.41	64.66	5.00
15	10	30	1	19.27	67.01	4.16
16	20	30	3	25.69	72.96	5.00
17	30	40	3	27.66	69.19	4.17

Swelling and Erosion studies

The swelling and erosion studies were performed to comprehend the influence of swelling and erosion behavior of the formulation on its drug release[20]. Matrix tablets were introduced into the dissolution apparatus under the standard set of condition as desided for drug release rate studies. The tablets were removed using small basket and the swollen weight of each tablet was determined. To determine the matrix erosion, swollen tablets were dried in a vaccum oven at 45^0C until to get constant weight.

For swelling index[21];

$$\text{Swelling Index} = \frac{(W_t - W_0)}{W_0} \quad X \quad 100$$

Where,

W_t is the weight of Tablet at time 't'.

W_o is the weight of Tablet at time t = 0.

For Erosion studies[22];

$$\text{Erosion studies} = \frac{\text{Original weight} - \text{Remaining dry weight}}{\text{Original weight}} \quad X \quad 100$$

Table 6. Different models used for dissolution study of optimized formulation

Model	Equation	R^2 value of Optimized formula
Zero order	$m_0 - m = kt$	0.8723
First order	ln m = kt	0.9022
Higuchi's Model	$m_o - m = kt1/2$	0.9878
Korsmeyer- Peppas	log (m0 _ m) =log K + nlog t	0.9920
Hixson- Crowell	$m_o^{1/3} - m^{1/3} = Kt$	0.8444

m_0 is the initial drug amount (100%); m is the amount of drug remaining at a specific time (calculated as % of m_0); k is the rate constant; and t is the time.

Data analysis and validation of optimization model

Statistical validation of the polynomial equation generated by Design Expert was established on the basis of ANOVA provision in the software. A total of 17 runs with five center points were generated. The models were evaluated in terms of statistically significant coefficients, standardized main effects (SME) and R^2 values. Various feasibility and grid searches were conducted to find the compositions of optimized formulation and various 3D response surface graphs were drawn by using Design Expert software. By intensive grid search performed over the whole experimental region, thirteen optimum checkpoint formulations were selected to validate the chosen experimental domain and polynomial equations[22]. The optimized checkpoint formulations were prepared and evaluated for various response properties. The resultant experimental values of the responses were quantitatively compared with that of the predicted values. Also, linear regression plots between actual and predicted values of the responses were produced using MS-Excel.

Table 7. Summary of results of regression analysis for response Y_1, Y_2 and Y_3

Models	R^2	Adjusted R^2	Predicted R^2	S.D	Remarks
Response(Y_1)	0.9036	0.9199	0.9591	0.72	-
Linear	0.9319	0.9911	0.9025	0.67	-
Second order Quadratic	0.9978	0.9876	0.9857	0.58	Suggested
Response(Y_2)	0.9232	0.9576	0.9450	0.58	-
Linear	0.9475	0.9615	0.9876	0.54	-
Second order Quadratic	0.9978	0.9990	0.9587	0.49	Suggested
Response(Y_3)	0.9416	0.9396	0.9459	0.45	-
Linear	0.9803	09792	0.9765	0.36	Suggested
Second order Quadratic	0.9315	0.9302	0.9219	0.43	-

Regression equation of fitted model*

$$Y_1 = 28.67 - 3.105X_1 + 2.217X_2 - 7.27X_3 + 0.335\,X_1X_3 - 0.045\,X_2X_3 + 0.59\,X_1^2 - 0.036\,X_2^2$$
$$Y_2 = 76.44 - 2.33X_1 + 0.916X_2 - 11.27X_3 + 0.24X_1X_3 + 0.161\,X_2X_3 + 0.049X_1^2 - 0.024X_2^2$$
$$Y_3 = 0.408 + 0.24X_1 + 0.102X_2 + 0.106X_3 - 0.0186X_1X_3$$

** only the terms with statistical significance are included*

Table 8. Composition of optimum checkpoint formulations, the predicted, experimental and residuals values of response variables and percentage prediction error

Composition (X_1%, X_2%, X3%)	Response variable	Experimental value	Predicted value	Residuals	Percentage prediction error
10%,30%,5%	Y_1(%)	25.9	26.35	-0.45	-1.70
	Y_2(%)	60.21	61.92	-1.71	-2.76
	Y_3(kg/cm^2)	4.5	4.51	-0.01	-0.22
30%,20%,3%	Y_1(%)	26.26	30.31	-4.05	-13.36
	Y_2(%)	72.26	73.70	-1.44	-1.92
	Y_3(kg/cm^2)	3.83	3.69	+0.14	-3.79
20%,20%,1%	Y_1(%)	23.24	19.64	+3.6	+18.32
	Y_2(%)	72.26	72.52	-0.26	-0.35
	Y_3(kg/cm^2)	4.0	4.06	-0.06	-1.47
20%,30%,3%	Y_1(%)	24.24	24.42	-0.18	-0.73
	Y_2(%)	66.82	66.82	0	0
	Y_3(kg/cm^2)	4.30	4.26	+0.04	-0.93
20%,20%,5%	Y_1(%)	25.17	28.11	-2.94	-10.45
	Y_2(%)	57.69	60.03	-2.34	-3.89
	Y_3(kg/cm^2)	4.5	4.60	-0.10	-2.17
20%,40%,1%	Y_1(%)	23.03	20.08	+3.22	+14.69
	Y_2(%)	65.1	62.75	-2.35	+3.74
	Y_3(kg/cm^2)	4.0	3.98	+0.02	+0.05
30%,30%,1%	Y_1(%)	26.13	25.67	+0.46	+1.79
	Y_2(%)	73.99	72.27	+1.72	+2.37
	Y_3(kg/cm^2)	3.67	3.84	-0.17	-4.42
30%,40%,3%	Y_1(%)	25.72	29.12	-3.4	-11.60
	Y_2(%)	65.23	69.28	-4.05	-5.80
	Y_3(kg/cm^2)	4.5	4.4	+0.1	+2.27
30%,30%,5%	Y_1(%)	52.77	45.76	+7.01	+15.30
	Y_2(%)	79.81	76.02	+3.79	+4.98
	Y_3(kg/cm^2)	4.16	4.29	-0.13	-3.30

20%,40%,5%	Y_1(%)	21.34	24.93	-3.59	-14.40
	Y_2(%)	63.42	63.15	+0.27	+0.42
	Y_3(kg/cm^2)	4.17	4.19	-0.02	-0.47
10%,20%,3%	Y_1(%)	27.93	24.5	+3.43	+14.0
	Y_2(%)	72.38	68.32	+4.06	+5.9
	Y_3(kg/cm^2)	5.0	4.98	+0.02	+0.40
10%,30%,1%	Y_1(%)	26.13	33.13	-4.06	-2.38
	Y_2(%)	73.99	77.78	-1.45	-4.80
	Y_3(kg/cm^2)	4.16	4.21	-0.06	-1.18
10%,40%,3%	Y_1(%)	27.02	22.96	+4.06	+17.68
	Y_2(%)	67.54	66.09	+1.45	+2.19
	Y_3(kg/cm^2)	3.67	3.73	-0.06	-1.60

Stability studies

Stability study of the optimized matrix tablets was carried out as per ICH guidelines at 25^{o}C±2 ^{o}C/60% ± 5%RH. Physical attributes of the tablets, appearance, % drug content and in-vitro drug release profiles were studied over a period of 3months.

RESULTS AND DISCUSSION

Drug content and physical evaluation

Drug content of the formulations was assayed spectrophotometrically at 235 nm. The drug in various formulations varied between 92.5% and 99.4% (average 95.13%). Tablet weights varied between 99.8 and 100.96 mg (average 100.32 mg), hardness between 3.5 and 5 kg/cm^2 (average 4.25 kg/cm^2), thickness between 3.16 and 3.62 mm(average 3.4mm) and friability ranged from 0.04% and 0.13% (average 0.40%). As the results of drug content and physical evaluation, all the formulations found to be practically within the official limits.

FTIR study

The FTIR analysis shows that there is no significant difference in the spectra of drug raw material, crushed powder of optimized tablet, and polymers and exhibited all characteristic bands (NH streching-3336, CH streching-2988, CO-1680, and NO streching-1529) as in the spectrum of the drug raw material (NH streching-3330, CH streching-2954, CO-1674, and NO streching-1529), excluding the possibility of any interaction, chemical and functional group change during the processing of tablet formulation.

***In-vitro* release kinetics**

To study the release mechanism of formulations, various dissolution models were applied to the *in-vitro* release profile of 17 runs. The kinetic model includes zero order, first order, higuchi, korsmeyer-peppas and Hixson-crowell model was evaluated by using PCP Disso software based on MS-Excel. The equations used to determine the appropriate models and presents the R^2 values for optimized formulation out of 17runs is shown in Table 6 and the release profile is shown in Figure 1. The overall curve fitting showed that drug release from optimized formulation from sustained release matrix tablet followed korsmeyer-peepas model (n=0.44 suggesting Fickian diffusion). As the dissolution progress the gradual swelling of outer layer creates proportionately new areas for drug diffusion. Since the matrix is hydrophilic, the permeation of dissolution medium takes place in the matrix and initiates dissolution of drug from the inner layer[23].

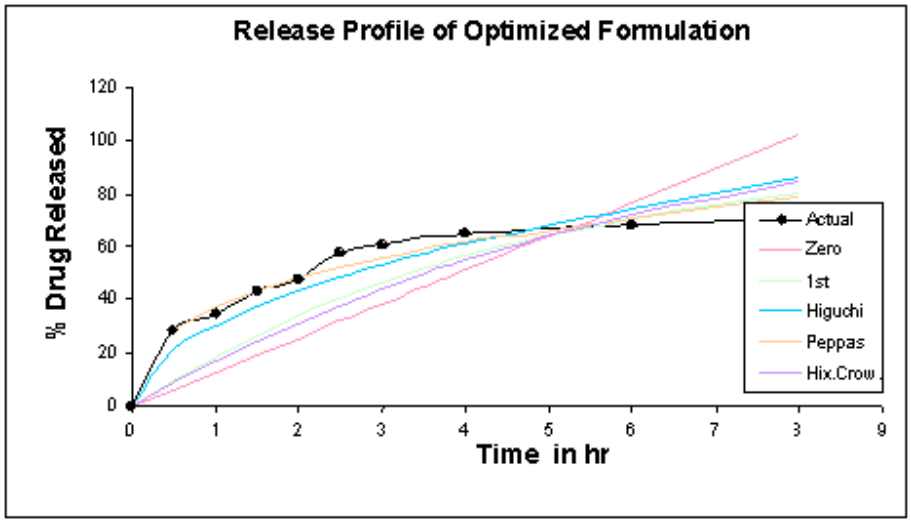

Figure 1. Different models used to study the dissolution profile of optimized formulation

Data fitting to the model

A three-factor, three-level Box-Behnken statistical experimental design as the RSM provides 17 runs and the independent variables and the responses for all 17 runs are given in Table 5. All batches showed the drug release at 1h (Y_1) and 8 h (Y_2) in the range between 19.27% - 27.93% and 60.03% - 79.81% respectively. The other response, hardness of the tablets Y_3 in the range between 3.67 - 5 kg/cm^2. All the responses observed for 17 formulations were simultaneously fitted to quadratic and second order when using Design Expert (State ease – Ver. 8.0.1) and the comparative values of R^2 and standard deviation are given in Table 7 along with the regression equation generated for each response. Responses Y_1, Y_2 and Y_3 were found to follow quadratic, quadratic and second order model respectively. Only statistically significant ($p < 0.05$) coefficients are included in the equations.

A positive value represents an effect that favors the optimization, while a negative value represents an inverse relationship between the factors and responses[24]. It is obvious that the HPMC K15M (X_1), HPMC E 10CR Prem.(X_2) and Sodium alginate (X_3) have positive and negative effects on the responses Y_1 and Y_2 in the following order;

HPMC E10CR Prem. (X_2) > HPMC K15 M (X_1) > Sod.alginate (X_3)

Coefficients with higher order terms or more than one factor term in the regression equation represent quadratic relationships or interaction terms, respectively. Dependent variables used at different levels in a formulation or when more than one factors are changed simultaneously, a factor can produce different degree of response. The interaction effect of X_1 was seen with X_2 and X_3 for response Y_2; and between X_1 and X_3 for response Y_3. X_2 also showed a higher quadratic effect as compared to X_1 on response Y_2.

Drug release at 1h (Y_1) and hardness of the tablets (Y_3) were found to fit the quadratic and second order models respectively. In Y_1 was mainly dependent upon the amount of HPMC

E10CR and HPMC K15M. For Y3, the critical parameters were found to be the HPMC K15M and the HPMC E10CR.

Standardized main effects and reliability of the models

Standardized Main Effects (SME) of all 17 runs was calculated by dividing the main effects with the standard error of the main effects[25], which is shown in Table 8. The larger SME value of X_3 suggested the paramount importance of Sodium alginate on drug release. R^2-value signifies the percentage of variability in responses that are fitted to the models. In the present study, the high R^2-value of >99% represents the reliability of the design. Additionally, the *p*-values of lack of fit were greater than 0.05, which further strengthened the reliability of the models.

Contour plots and response surface analysis

Two dimensional contour plots and 3-D response surface plots are presented in Figure 2-7, which are very useful to study the interaction effects of the factors on the responses. These types of plot show the effect of two factors on response at one time[24]. All the Figures, the third factor was kept at zero level. Figure 2 and 3 exhibit a nearly linear relationship of factor X_2 and X_3 with factors in the form of almost straight lines. However factor X_3 and X_2 have non-linear relationship shown in Figure 4. Response surface plots show the relationship between these factors even more clearly. Figure 5, shows the drug release at 8 h is increases when HPMCK15M decreases and HPMC E10CR increases, so that the percentage drug release gives more release, when there is mid concentrations of X_1 and X_2. This indicates slight-linear between the factor X_1 and X_2. Figure 6 and 7 shows an increasing trend for Y_2 upon HPMC K15M decreases with increasing amount of sodium alginate and also upon HPMC E10 CR increases with sodium alginate.

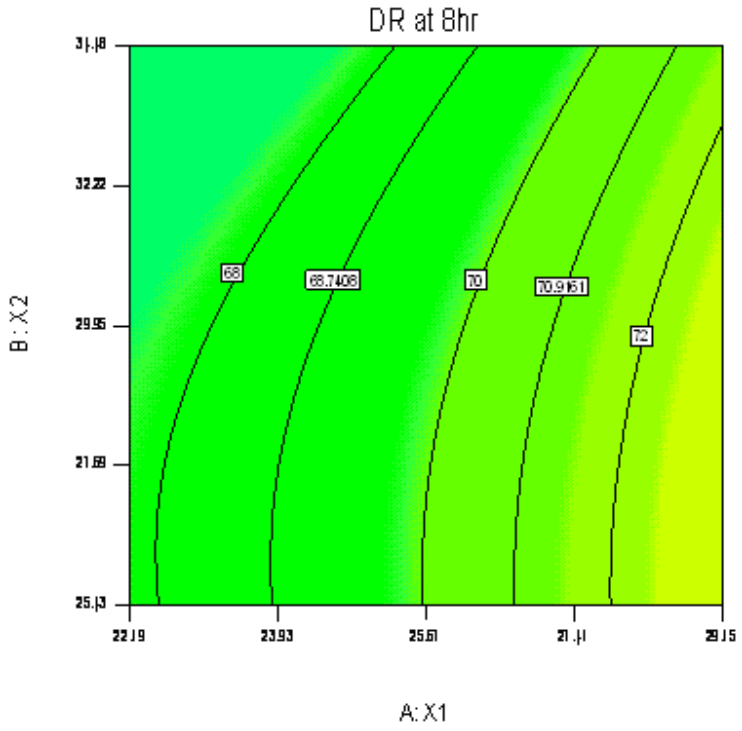

Figure 2. Contour plot showing the effect of HPMC K15M(X_1) and HPMC E10(X_2) on response Y_2

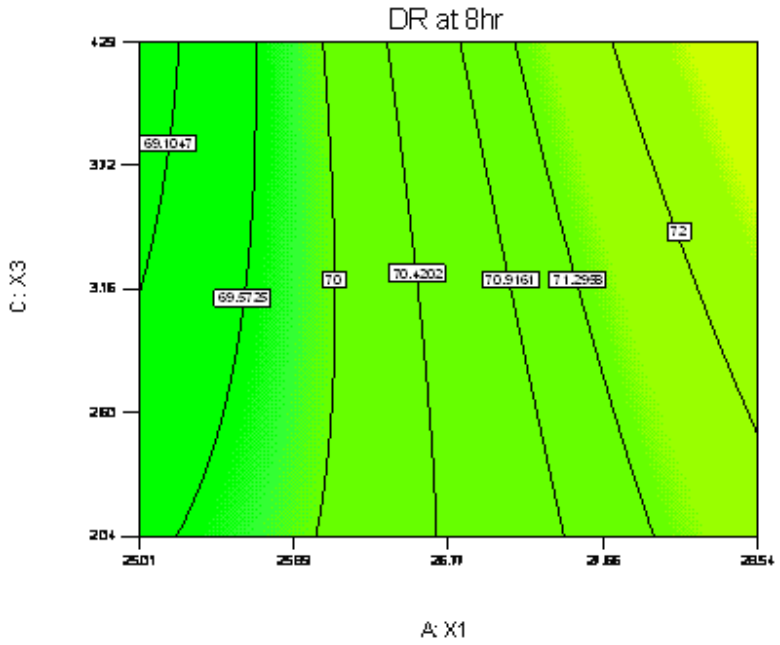

Figure 3. Contour plot showing the effect of HPMC K15M(X_1) and Sodium alginate(X_3) on response Y_2

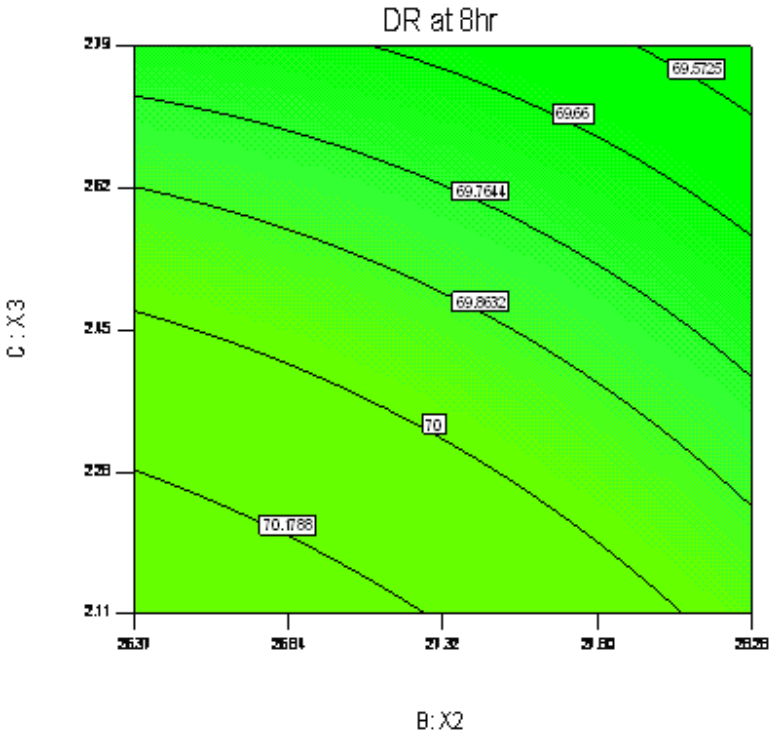

Figure 4. Contour plot showing the effect of HPMC E10(X_2) and Sodium alginate(X_3) on response Y_2

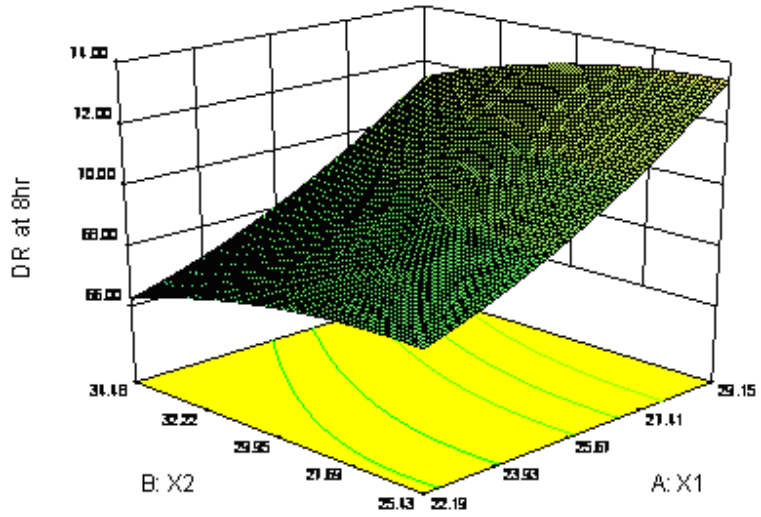

Figure 5. Response surface plots showing the effect of HPMCK15M(X_1) and HPMCE10(X_2) on response Y_2

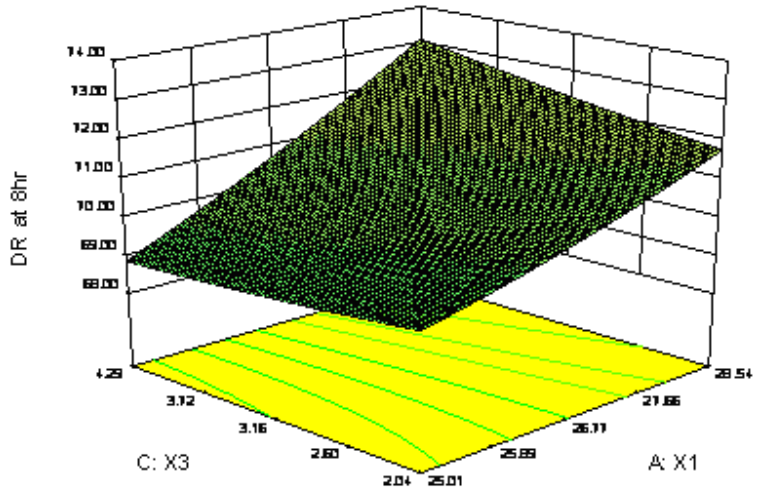

Figure 6. Response surface plots showing the effect of HPMCK15M(X_1) and Sodium alginate(X_3) on response Y_2

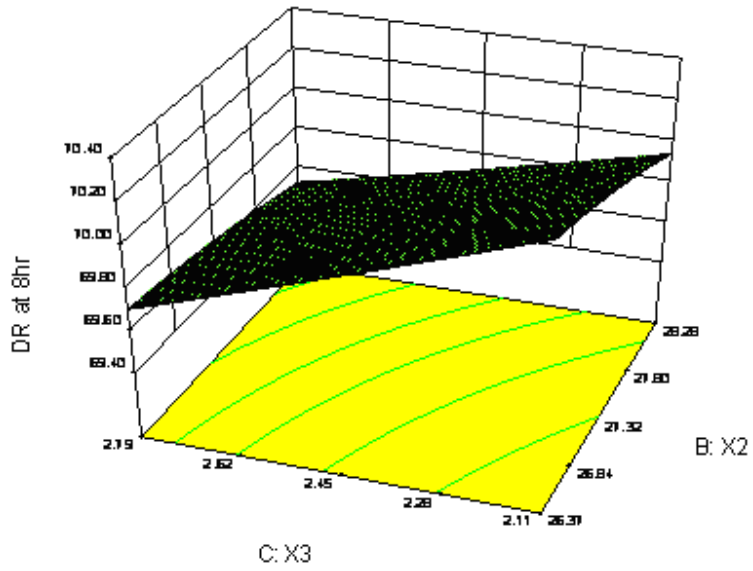

Figure 7. Response surface plots showing the effect of HPMC E10(X_2) and Sodium alginate(X_3) on response Y_2

Optimization

The optimum formulation was selected based on the criteria of attaining the maximum hardness for tablets and applying constraints on Y_1 ($20 \leq Y_1 \leq 25$) and Y_2 ($70 \leq Y_2 \leq 75$). Upon 'trading off' various response variables and comprehensive evaluation of feasibility search and exhaustive grid search, the formulation composition with polymer levels of HPMC K15 M (20 mg), HPMC E10 CR Prem. (30mg), and Sodium alginate (3mg) was found to fulfill the maximum requirement of an optimum sustained release matrix formulation, because of better regulation of percentage drug release in 1h and 8 h. The optimized formulation was found to be released about 90% of drug in sustained manner for 12 h. Study of the *in-vitro* release profiles in phosphate buffer (pH6.8) for 8 h, of the optimized formulation showed 23.69% of drug release at 1h followed by a gradual release phase for about 8 h, which is shown in Figure 1 (actual curve). The release pattern of the optimized formulation was best fitted to Korsmeyer-Peppas kinetics (sustained release phase) with R^2 values of 0.9920. The value of n = 0.44 suggested the release to be primarily by Fickian diffusion.

Validation of RSM results

The 13 checkpoint formulations obtained from the Design expert optimization solutions shows the composition of optimum checkpoint formulations, their predicted and experimental values of all the response variables, and the percentage error and also residuals in prognosis[26] which is shown Table 8. Linear correlation plots between the actual and the predicted response variables were plotted and the residual plots, showing the scatter of the residuals versus actual values. The residual versus observed response plot and predicted versus actual linear correlation plots of Y_1, Y_2 and Y_3 are presented in Figure 8-13 respectively. For validation of RSM results, the experimental values of the responses were compared with that of the anticipated values and the prediction error was found to vary between –14.40% and +17.68%. The low magnitudes of error as well as the significant values of R^2 in the present investigation prove the high prognostic ability of the RSM.

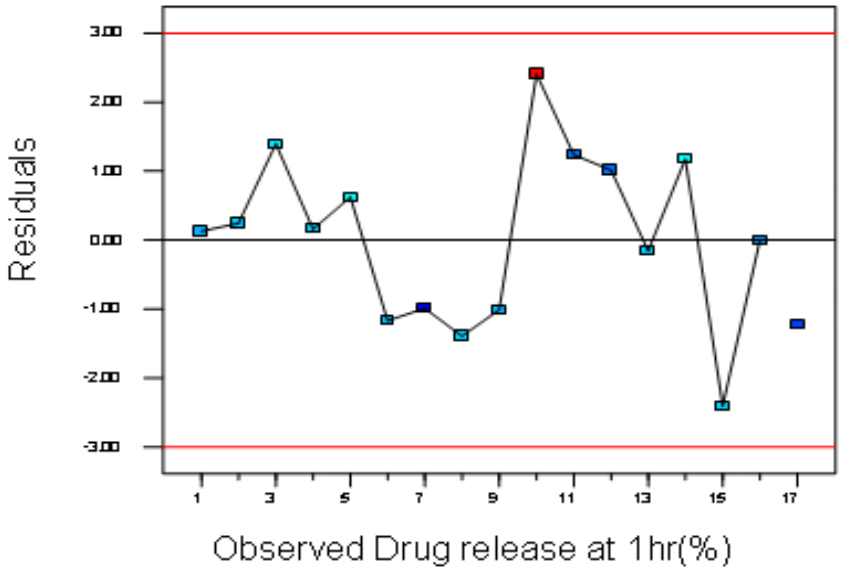

Figure 8. Linear correlation plot between residuals versus observed response for Y_1

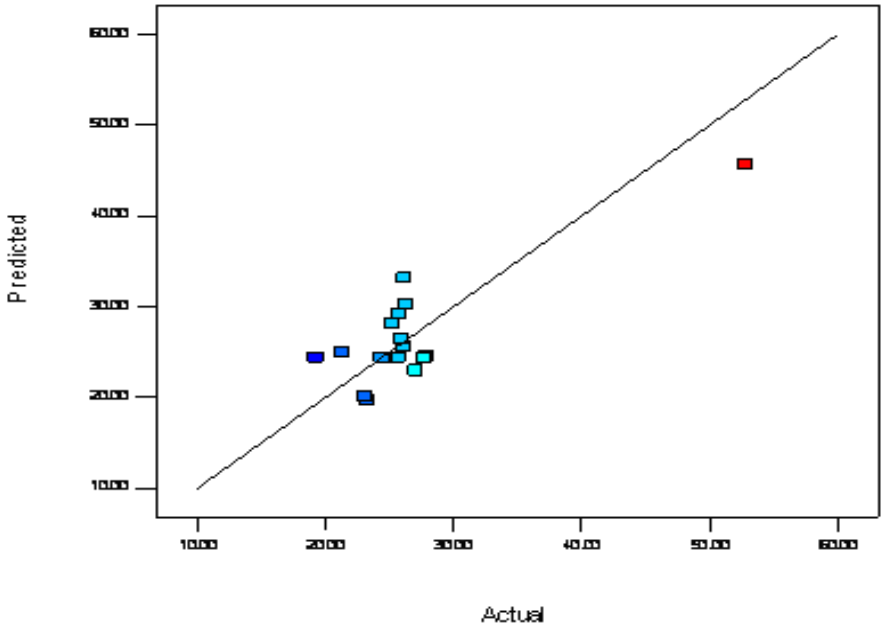

Figure 9. Linear correlation plot between predicted versus actual response for Y_1

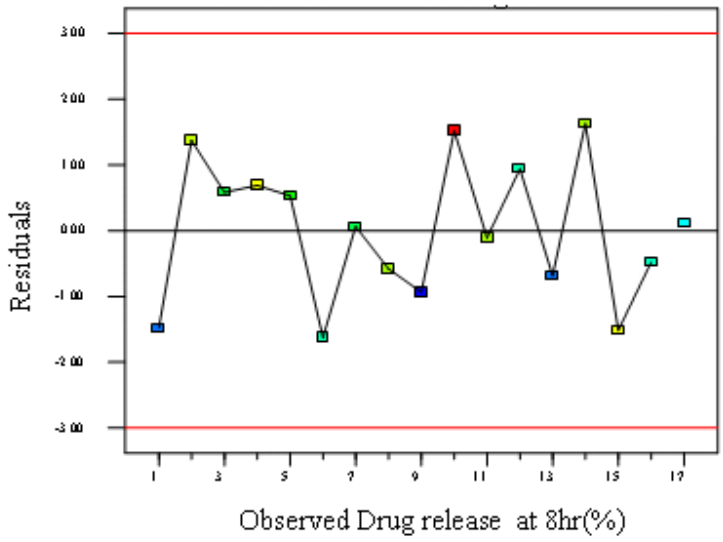

Figure 10. Linear correlation plot between residuals versus observed response for Y_2

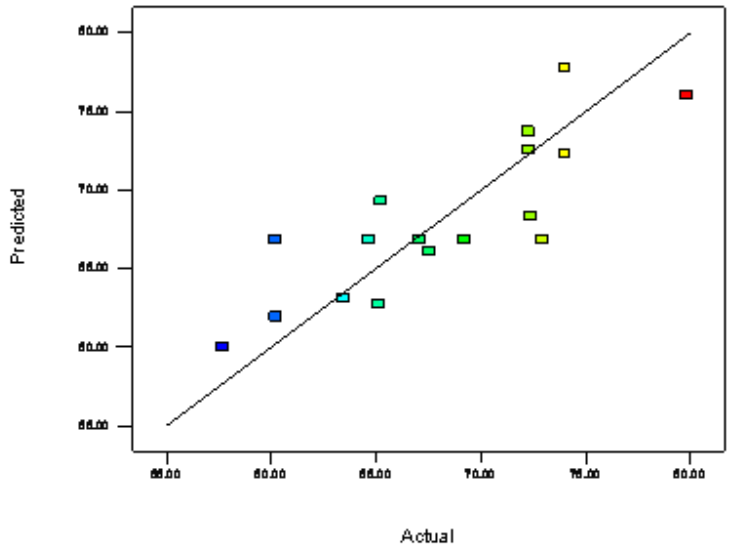

Figure 11. Linear correlation plot between predicted versus actual response for Y_2

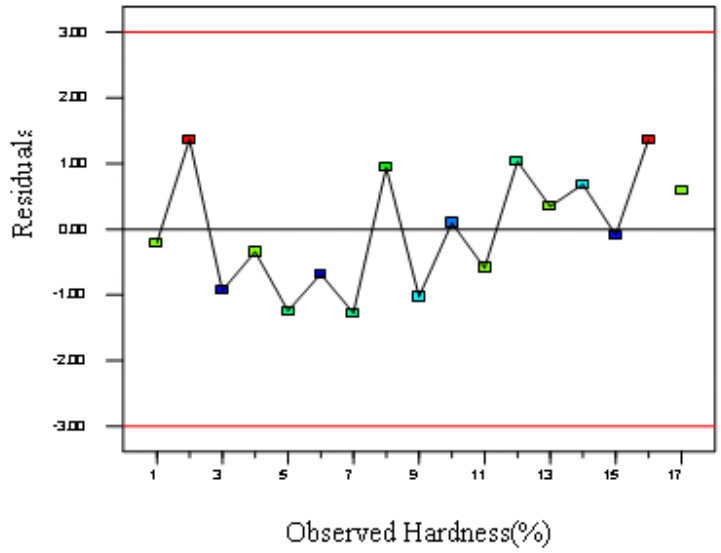

Figure 12. Linear correlation plot between residuals versus observed response for Y_3

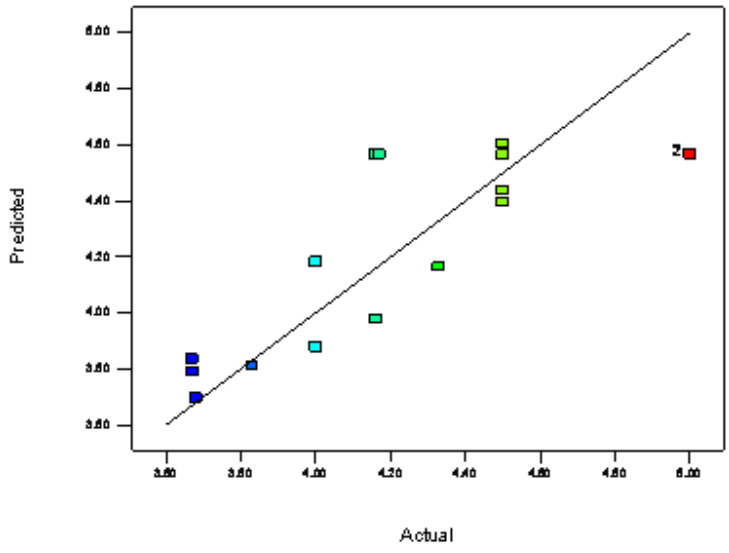

Figure 13. Linear correlation plot between predicted versus actual response for Y_3

Swelling and erosion studies

The swelling index and erosion studies were calculated for the validated 13 formulations. Increased percentage swelling index of the tablets was observed up to 4 h due to weight gain by tablets. Later, the weight gain was decreased gradually due to dissolution medium and slow erosion of the gelled layer up to 8 h. Erosion of the optimized formulation after 8 h was found to be 23.3%, this low erosion due to the polymer concentration used in the formulation. The percentage swelling index of the optimized formulation is shown in Figure 14.

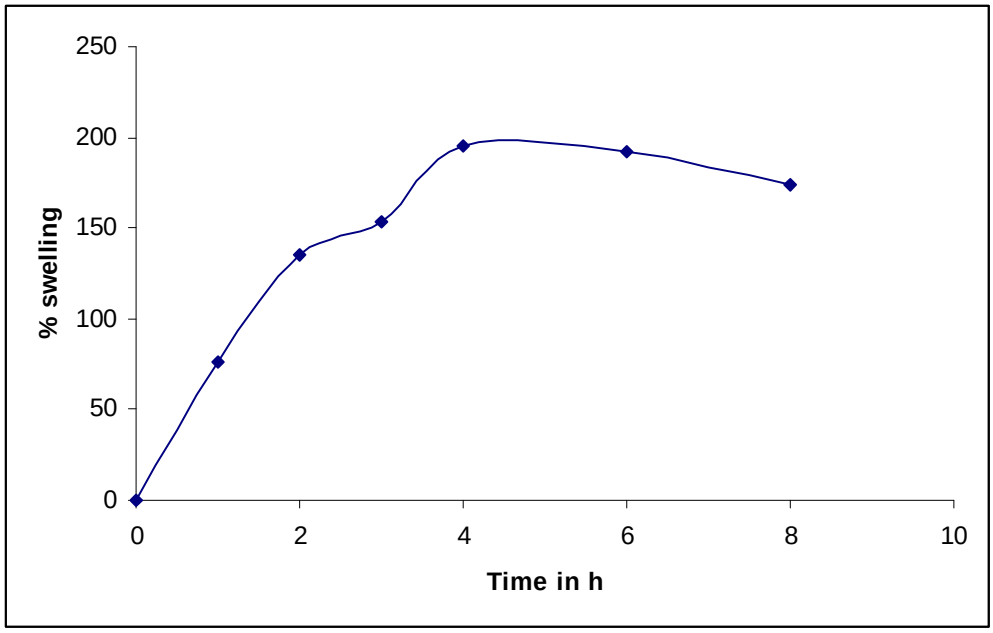

Figure 14. Percentage swelling index of the optimized formulation

Stability studies

Stability studies of the optimized formulation under accelerated storage conditions as per ICH guidelines did not reveal any degradation of the drug and changes in the in vitro release profiles of the optimized formulation after storage for 3 months were statistically insignificant as compared to the refrigeration control sample (ANOVA, $p > 0.05$).

CONCLUSION

Hydrophilic matrix system of Nifedipine with HPMC K15M, HPMC E10CR Prem. and Sodium alginate were prepared using direct compression technique and optimized using a three-factor, three-level response surface methodology (Box Behnken design) with 17 runs. The quadratic response surface methodology studied for the release rate helped in understanding the interaction effects between the combination and ratio of the three polymers. The quantitative effect of these factors at different levels on the release rate could be predicted by using polynomial equations. Linearity observed between the actual and predicted values of the response variables suggested the predictive ability of the response surface methodology design. FTIR studies combined with the stability study of the optimized formulation proved the reliability of the developed hydrophilic sustained release matrix tablets. Thus, high degree of prediction obtained using response surface methodology is quite efficient in optimizing drug delivery systems that exhibit non-linearity in responses.

Acknowledgement

Authors thankful to The Chairman, Karpagam University, Coimbatore, India for providing Lab. facilities and encouragement during this research.

REFERENCES

[1] Gupta R., *J Hum Hyperten*., **2004**, 18,73.
[2] Sorkin E.M., Clussold S.P., and Brogden R.N., *Drugs*, **1985**, 30, 180.
[3] J.S. Grundy, R.T. Foster, *Clin.pharmacokin*., **1996,** 30, 28–51.
[4] H. Bode, E. Brendel, G. Ahr, U. Fuhr, S. Harder, A.H. *Eur. J. Pharmacol*.,**1996**, 195–201.
[5] C.H. Kleinbloesem, P. van Brummelen, M. Danhof, H.Faber, J. Urquhart, D.D. Breimer, *Clin. Pharmacol. Ther*., **1987**, 41, 26–30.
[6] Theeuwes F. Oros, *Drug Dev Ind Pharm*., **1983**, 9, 1331-1357.
[7] Vazquez MJ, Perez-Marcos B, Gomez-Amoza JL, Matrinez-Pacheco R, Souto C, Concheiro A, *Drug Dev Ind Pharm*., **1992**, 18, 1355-75.
[8] Desai SJ, Singh P, Simonelli A P,Higuchi WI; *J Pharm Sci*., **1966**, 55, 1224.
[9] Li CL, Martini LG, Ford JL, Roberts M; *J Pharm Pharmacol*., **2005**, 57, 533.
[10] P. Dayal, V. Pillay, R.J. Babu, M. Singh, *AAPS Pharm. Sci. Tech*., **2005**, 6, E573–E585.
[11] B. Singh, S.K. Chakkal, N. Ahuja, *AAPS Pharm. Sci. Tech*., **2006**, 7, E1–E9.
[12] S.K. Singh, J. Dodge, M.J. Durrani, M.A. Khan, *Int. J. Pharm*., **1995**, 125, 243–255.
[13] A. Boza, Y. De la Cruz, G. Jordan, U. Jauregui-Haza, A. Aleman, I.Caraballo, *Drug Dev. Ind. Pharm.*, **2000**, 26, 1303–1307.
[14] G.E.P. Box, K.B. Wilson, *R. Stat. Soc*., **1951**, 13, 1–12.
[15] C. Sa´nchez-Lafuente, S. Furlanetto, M. Ferna´ndez-Are´valo, J.Alvarez-Fuentes, A.M. Rabasco, M.T. Faucci, S. Pinzauti, P. Mura, *Int. J. Pharm.*, **2002**, 237, 107–118.
[16] A. Palamakula, M.T.H. Nutan, M.A. Khan, *APPS Pharm. Sci. Tech*., **2004**, 5, 1–8.
[17] R. Ragonese, M. Macka, J. Hughes, P. Petocz, *J.Pharm. Biomed. Anal.*, **2002**, 27, 995–1007.
[18] S. Govender, V. Pillay, D.J. Chetty, S.Y. Essack, C.M. Dangor, T.Govender, *Int. J. Pharm*., **2005**, 306, 24–40.
[19] G.E.P. Box, D.W.Behnken, *Technometrics* ., **1960**, 2, 455-475.
[20] Al-tanni M, Tash toush BM; *AAPS Pharm Sci Tech*, **2003**, 4, E3.
[21] P.G.Yeole U.C.Galgatte,I.B.Babla and P.D.Nakhat; *Ind J Pharm Sci*., **2006**, 68(2), 185-189.
[22] Shruti chopra,Gayathri V.Patli, Sanjay K.Motwani; *Eur J Pharm. Biopharm*., **2007**, 66, 73-82.
[23] A.T. Pham, P.I. Lee, *Pharm. Res.* **1994**, 11, 1379–1385.
[24] Shruti chopra, sanjay K.Motwani, Zeenat Iqbal, Sushma Talegaonkar, Farhan J.Shmad, Roop K. Khar; *Eur J Pharm. Biopharm*., **2007**, 67, 120-131.
[25] M.T.H. Nutan, M.S. Soliman, E.I. Taha, M.A. Khan, *Int. J. Pharm*., **2005**, 294, 89–101.
[26] Anees A.Karnachi, Mansoor A.Khan, *Int J Pharm.*, **1996**, 131, 9-17